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| APPLICATION NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKET NO. |
|--------------------|-------------|-----------------------|---------------------|
|--------------------|-------------|-----------------------|---------------------|

08/468,161 06/06/95 DEFEO-JONES

D 192531B

EXAMINER

HM12/0210

DAVID A MUTHARD
PATENT DEPARTMENT
MERCK & CO INC
PO BOX 2000
RAHWAY NJ 07065-0907

DELAEROIX MUIRHEI, C

ART UNIT PAPER NUMBER

1614

25

DATE MAILED:

02/10/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

NOTICE OF ALLOWABILITY

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

☒ This communication is responsive to amendment and terminal disclaimer of 11/10/99

☒ The allowed claim(s) is/are 21, 13-19

☐ The drawings filed on _____ are acceptable.

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE **THREE MONTHS** FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☒ Applicant MUST submit NEW FORMAL DRAWINGS

☐ because the originally filed drawings were declared by applicant to be informal.

☒ including changes required by the Notice of Draftperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. 6

☐ including changes required by the proposed drawing correction filed on _____, which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftperson.

☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). # 20

☐ Notice of Draftperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☐ Interview Summary, PTO-413

☐ Examiner's Amendment/Comment

☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

☐ Examiner's Statement of Reasons for Allowance

Wayne C. Jones
WAYNE C. JONES
PATENT EXAMINER, 1614

In Claim 13, page 118, line 21, delete the phrase "Claim 12" and replace it with the phrase -- Claim 21. --

In Claim 14, page 119, line 1, delete the phrase "Claim 12" and replace it with the phrase -- Claim 21. --

In Claim 15, page 119, line 28, delete the phrase "Claim 12" and replace it with the phrase -- Claim 21. --

In Claim 16, page 119, line 32, delete the phrase "Claim 12" and replace it with the phrase -- Claim 21. --

REMARKS

Claims 12-19 are pending in the instant application. The claims have been finally rejected for the reasons noted hereinbelow. Applicants respectfully traverse the rejections as set forth by the Examiner and request reconsideration of the application in light of the amendments hereinabove and the following remarks.

Applicants note that the claims now being examined are directed to cytotoxic conjugates that comprise oligopeptides that can be selectively proteolytically cleaved by free PSA that are useful in the treatment of prostate cancer.

The Examiner has maintained the provisional rejection of Claims 12-19 under the judicially created doctrine of obviousness-type double patenting as being unpatenable over Claims 20-23 of copending application 08/540,412. Applicants respectfully note that they have filed a terminal disclaimer in the '412 application over the instant application (copy attached), and that in light of the terminal disclaimer the rejection under the judicially created doctrine of obviousness-type double patenting is now moot and should be withdrawn.

The Examiner has maintained the rejection of Claims 12-19 under 35 U.S.C. §103 as being obvious over the previously discussed Lilja et al scientific publication in view of the Kaneko et al. U.S. Pat. No. 5,349,066. The Examiner suggests that the disclosures in the Lilja et al reference read on the oligopeptide portion of the instant invention. Applicants have noted before the clear limitation to the peptide component of the claimed conjugates in the specification as filed on page 9, lines 9-10. Applicants have now rewritten Claim 12 as new

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Claim 21, wherein semenogelin I and II are expressly excluded from the definition of oligopeptide. Applicants respectfully contend that such an amendment does not add new matter since the exclusion of semenogelin I and II from the oligomers that define oligopeptide is present in the specification as filed. Applicants thus respectfully request that the Examiner enter the amendment.

Applicants note that in light of the amendment, the Lilja et al. reference does not read on the oligopeptides of the instant claims, nor do Lilja et al. suggest that there are several smaller oligopeptides that are also selectively cleaved by free PSA. And, as noted by the Examiner, there is no teaching or suggestion by Lilja et al. that any peptides, especially not truncated and significantly modified portions of semenogelin I and II, should be conjugated to a cytotoxic agent.

Applicants note that the Kaneko et al. patent describes conjugates that comprise a cytotoxic molecule linked by a bifunctional compound to a molecule that is reactive with a target cell population. Applicants note that the description in the Kaneko patent of a targeting molecule is limited to antibody proteins and ligands (col. 9, lines 29-31). Applicants note that the "antibodies" and "ligands" are described in the patent as binding to tumor associated antigens, binding to virus or other pathogen associated antigens, or binding specifically to a receptor associated with the cell surface of a target cell population (col. 11, lines 5-51). Applicants note that there is no description or suggestion in the Kaneko et al. patent that such conjugates be modified to comprise, instead of a ligand or antibody, an oligopeptide that is selectively cleaved by an enzyme that is intimately associated with the target cell population.

Applicants respectfully note that the release of the cytotoxic reagent as described in the Kaneko et al. patent depends on cleavage of an acid sensitive bond of the conjugate within the target cell (col. 12 lines 33-41). Applicants again note that the conjugates of the instant invention are selectively cleaved by enzymatically active free PSA in the vicinity of the target prostate cancer cell. Applicants respectfully contend that there is no requirement that the conjugates of the instant invention actually come into contact with acid in order to liberate the cytotoxic agent. Applicants also note that there is no suggestion by Kaneko et al. that the novel "bifunctional compounds" of their invention should not be present in a conjugate, as is the case with the instant invention which contains no such bifunctional compound.

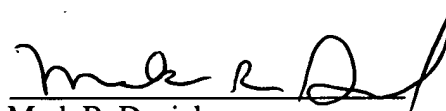
Applicants finally note that there is no teaching in the Kaneko et al. patent that such inventions as disclosed therein should be combined with the teaching of Lilja et al.

Therefore, Applicants strongly content that, in spite of the description in the prior art of Semenogellin I and II and of conjugates of cytotoxic agents and targeting molecules, the conjugates claimed in the instant application that rely on selective cleavage of a oligopeptide portion of a cytotoxic conjugate by an enzyme is not taught or suggested by those references, and a person of ordinary skill in the art would not be motivated to make such a conjugate based on those disclosures. Applicants therefore contend that the Examiner's rejection under 35 U.S.C. §103 as being obvious over the previously discussed Lilja et al scientific publication in view of the Kaneko et al. U.S. Pat. is untenable, especially in light of the express exclusion in new Claim 21 of semenogelin I and II from the definition of oligopeptide, and should be withdrawn.

Applicants respectfully contend that the Examiner's remaining rejections of the instant application have been addressed and obviated by the above amendments and remarks, and that Claims 13-19 as filed and amended and new Claim 21 are allowable and an early Notice of Allowance is earnestly solicited.

Respectfully submitted,

By:



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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

HM12/0210

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| APPLICATION NO. | FILING DATE | TOTAL CLAIMS | EXAMINER AND GROUP ART UNIT | DATE MAILED |
|-----------------------|--------------|---------------------------|-----------------------------|---------------|
| 08/468,161 | 06/06/95 | 008 | DELACROIX MUIRHEI, C | 1614 02/10/00 |
| First Named Applicant | DEFEO-JONES, | 35 USC 154(b) term ext. = | 0 Days. | |

TITLE OF INVENTION NOVEL PEPTIDES

| ATTY'S DOCKET NO. | CLASS-SUBCLASS | BATCH NO. | APPLN. TYPE | SMALL ENTITY | FEE DUE | DATE DUE |
|-------------------|----------------|-------------|-------------|--------------|-----------|----------|
| 1 | 192531B | 530-322.000 | H97 UTILITY | NO | \$1210.00 | 05/10/00 |

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

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- B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

- A. Pay FEE DUE shown above, or
- B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give application number and batch number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

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